Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER D—DRUGS FOR HUMAN USE

[Docket No. 76N-0384]

PART 310—NEW DRUGS

Requirement for Labeling Directed to the Patient

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The agency is issuing final regulations to require patient labeling for all prescription estrogenic drug products for general use. The new regulation specifies the kind of information to be contained in the patient labeling and how it is to be made available to the patient. The regulation does not apply to estrogen-progestagen oral contraceptives and oral diethylstilbestrol (DES) products intended for postcoital contraception.

EFFECTIVE DATE: September 20, 1977.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of September 29, 1976 (41 FR 43108) the Commissioner of Food and Drugs proposed new requirements for patient labeling for estrogens for general use. Interested persons were invited to submit comments on the proposal by November 29, 1976. More than 300 comments were received. Comments came from drug establishments, drug trade associations, professional societies, consumer groups, and individual citizens. A summary of the comments and the Commissioner's response are set forth below:

1. *Statutory authority.* Several comments contend that the Food and Drug Administration (FDA) lacks the requisite legal authority to require patient labeling. The comments note that the proposal to add new § 310.515 (21 CFR 310.515) cites sections 502, 505 and 701 (a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352, 355, 371(a)) as authority for requiring patient labeling for estrogens, and none of these sections provides such authority. The comments also refer to congressional intent expressed at the time of enactment of section 503(b) of the act, together with previous FDA statements on the subject, to urge that the patient labeling proposal is without statutory basis. Specifically, they argue that the enactment of section 503(b) (2) of the act in 1951 reflected a clear understanding by Congress that prescription drugs need not bear labeling containing directions for patient use and that this section exempts prescription drugs at the time the drug is dispensed by the pharmacist from any requirement that the labeling bear adequate directions for use and warnings under section 502(f) of the act. They also point to two bills introduced but not enacted in the last session of Congress that would have permitted patient labeling under varying circumstances.

The comments contend that sections 505 and 701(a) of the act contain no language authorizing promulgation of a patient labeling regulation. It is claimed that section 505 of the act contains nothing suggesting or pertaining to authority to require patient labeling for new drugs while section 701(a) of the act provides FDA with only general rule making authority, and allows for promulgation of regulations only on subjects that are specifically covered by some other section of the act.

The Commissioner disagrees with these contentions. The Food and Drug Administration's legal authority for requiring patient labeling was explained in detail in paragraph 4 of the preamble to the proposed new format for prescription drug labeling published in the FEDERAL REGISTER of April 7, 1975 (40 FR 15392). The Commissioner affirms that explanation. Section 505 of the act provides that a new drug application (NDA) may be approved only if a new drug is shown to be safe and effective in use under the conditions set out in its labeling, and section 201(p) of the act (21 U.S.C. 321(p)) similarly provides an exemption from the requirement of an NDA only if the drug is generally recognized as safe and effective under the conditions of use set out in its labeling. Moreover, both sections 502(a) of the act and section 505(d) of the act prohibit prescription drug labeling that is false or misleading in any particular, and section 201(n) of the act explicitly provides that the failure to reveal material facts can be misleading. Accordingly, the act requires the Commissioner to make a determination that the information contained in the labeling for a prescription drug is sufficient to assure the safe and effective use of that drug by consumers. The Commissioner concludes that such determination may well require specific information to be provided to consumers about the drug, as has already been required for the oral contraceptives in § 310.501 (21 CFR 310.501).

The primary purpose of the provision in section 503(b) (2) of the act exempting a prescription drug from adequate directions for use and warnings is to avoid self-diagnosis and self-administration of drugs that require professional supervision for safe use. Requiring a prescription drug product to contain printed patient information does not contradict this purpose. For estrogens, such information will inform the patient of the advantages and risks associated with the use of these drugs and will ensure safe and effective use of the drug after it has been prescribed by the physician. Nothing in the legislative history of section 503(b) or in any other section of the act suggests that Congress intended to preclude a requirement of labeling directed to the patient that promotes safe and effective use of the drug.

The introduction of two bills in the last session of Congress to provide for patient labeling is not an indication that Congress believes that FDA lacks statutory authority to require patient labeling for prescription drugs absent such legislation. The Commissioner believes that these bills have resulted from the recognition by certain members of Congress that arguments such as have been raised by the comments have been and will continue to be made. Legislation specifically providing for patient labeling would resolve questions about the agency's authority once and for all.

The Commissioner also disagrees with the contention that section 701(a) of the act allows only for the promulgation of substantive regulations on subjects that are specifically authorized by some other section of the act. Rather, section 701(a) of the act empowers the Commissioner to promulgate substantive rules to facilitate enforcement of the act. *United States* v. *Nova Scotia*, 417 F. Supp. 1304 (E.D. NY., August 17, 1976); *National Nutritional Foods Association* v. *Weinberger*, 512 F. 2d 688 (2d Cir. 1975); *Weinberger* v. *Hynson, Wescott and Dunning, Inc.*, 412 U.S. 609 (1973); *Ciba Corp.* v. *Weinberger*, 412 U.S. 645 (1973). Accordingly, the Commissioner concludes that a regulation issued pursuant to section 701(a) of the act may lawfully establish a requirement for patient labeling for a prescription drug product.

2. *Consistency of procedures employed by FDA with section 505 of the act.* Several comments allege that the procedure followed by FDA is inconsistent with section 505 of the act. They note that the products to which the proposal would apply are subject to approved NDA's and argue that under section 505(d)(6) of the act, the agency's approval of those applications was based in part on a determination that labeling submitted with them, including physician labeling, was not "false or misleading in any particular." They insist that section 505(e) of the act provides the only procedure by which FDA may withdraw approval for an NDA and that withdrawal must be based upon a determination that labeling contained in the NDA is false or misleading in light of "new information." The comments argue that FDA cannot circumvent this procedure by issuing a notice of its intent to treat as misbranded drugs those whose labeling is in full compliance with NDA's that have been approved by the agency.

The Commissioner disagrees. Although section 505(e) of the act provides that FDA may withdraw approval of an NDA if new information demonstrates that the approved labeling is false or misleading, section 505 of the act is not the exclusive method for regulating new drugs. All drug products, including those subject to section 505, are subject to the adulteration and misbranding provision of sections 501 and 502 of the act. If a new drug product is misbranded under section 502(a) of the act, the Commissioner has the option to proceed with enforcement action under either section 502 or section 505 or both. Proceeding

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under section 502 is in no way inconsistent with section 505.

3. *Infringement upon the practice of medicine.* Several comments alleged that the proposed regulation would result in a direct and substantial Federal involvement in the patient/physician relationship and would be an infringement upon the practice of medicine. The comments argued that under the traditional patient/physician relationship, the physician provides such information to the patient concerning drug therapy as the physician considers appropriate. The language of section 503(b) of the act, it was suggested, reflects this relationship. The comments argued further that intrusion into the practice of medicine is compounded by statements in the patient labeling (see the FEDERAL REGISTER of October 29, 1976 (41 FR 47576)) that encourage the patient to ask the doctor or pharmacist for the package insert (physician labeling), which by definition is directed to trained professionals. This, it is argued, will unduly increase a patient's concern about the drug and the therapy unless the patient is fully conversant with complicated medical and scientific terminology.

The Commissioner believes that the findings linking postmenopausal estrogen use to endometrial cancer, the reports of an association between intrauterine exposure to estrogens and congenital anomalies, and the findings of an increased risk of vaginal cancer in adolescent daughters exposed in utero to an estrogen (DES) must not only be carefully considered by physicians who prescribe these drugs, but also by patients who take them. The advantages and risks associated with the use of these products are of a type that can and should be assessed by patients.

The Commissioner does not agree that the requirement for patient labeling interferes with the physician/patient relationship or infringes on the practice of medicine. Indeed, by directing the patient to consult with her physician the labeling requirement explicitly recognizes the primary responsibility of the prescribing physician to convey to the patient, information regarding prescribed drugs. This regulation, therefore, is not intended to preempt the physician's responsibility, nor will it have that effect. Rather, in situations where physicians are conscientious in describing the relative benefits and risks of these drugs with their patients, the patient labeling will simply reinforce what the physician has explained to the patient and serve as a written reminder that can be referred to by the patient during the course of therapy.

At the same time, the Commissioner recognizes that information regarding the benefits and risks of estrogen drug products is sometimes not fully provided by physicians. Even when it is, it is likely to be given verbally and may thus be misinterpreted or forgotten by patients. For these reasons it is additionally necessary that these drugs contain patient labeling. But under no circumstances is the presence of the labeling intended to supersede the role of the physician in informing the patient or to interfere in any way with communications between the physician and his or her patients.

The statement in the patient labeling that refers to the physician insert is intended primarily to advise the patient that such an insert exists and that it is available to the patient if the patient is interested in reading it. The Commissioner believes that it is necessary and proper to inform patients that they may obtain additional information on the use of these drugs if they so desire. The existence and availability of such inserts is already known to many patients and the Commissioner believes the information should be available equally to those patients who are less informed. Moreover, as the Commissioner has made patient labeling selective in scope—it does not attempt to describe all the information that is included in physician labeling—he would view as inappropriate the failure to advise patients that the patient labeling insert does not contain all the known information on the drug. Therefore, the Commissioner concludes that the reference to the physician labeling should be retained in patient labeling.

4. *Product liability consequences.* Several comments contend that patient labeling could have a substantial adverse effect on the liability of manufacturers by imposing a standard of "absolute" liability. The comments explain that in recent years there has been a trend among the courts to adopt the concept of "strict liability" as expressed in the "Restatement (Second) of Torts" (a highly regarded but unofficial legal treatise). The comments argue that under 402(A) of the Restatement, a manufacturer may be held strictly liable for personal injury to a consumer without regard to negligence on the part of the manufacturer if injury follows the normal and reasonable use of the product. The comments claim that when applied to prescription drugs, owing to the inherent nature of such products, the doctrine will result in the application on manufacturers of an "absolute liability" standard.

The Commissioner does not agree that the imposition of a requirement for patient labeling will necessarily affect adversely the standard of civil tort liability that is imposed on drug manufacturers. Whether or not a manufacturer is to be held liable in a given situation will depend upon the facts surrounding the manufacture, sale, and use of the drug product. It will also depend on the nature of the injury and the applicable civil law. Moreover, the Commissioner believes that giving patients information on the hazards associated with estrogen drug products will as likely result in reduced potential manufacturer liability, owing to improved patient compliance and a corresponding decrease in drug-induced injury. In any event, however, whether particular labeling may alter a manufacturer's liability in a given instance cannot be considered as a dispositive factor by the Commissioner in reaching a decision on the proposal. The Commissioner concludes that to assure the safe and effective use of estrogen products it is necessary that the patient be provided with certain specific information in the form of patient labeling, in addition to the instructions normally received from the prescribing physician. The Commissioner believes it proper that a regulation requiring such labeling be promulgated, notwithstanding the possibility that it may have an effect on a manufacturer's liability in isolated instances.

5. *Consistency with previously announced FDA policy.* Several comments contend that the finalization of this proposal would be inconsistent with announced FDA policy. They point to the statement in the FEDERAL REGISTER of November 7, 1975 (40 FR 52075) in which FDA announced its intent to consider the patient labeling concept in depth, prior to implementation. Because of this statement and other activities in this area undertaken by FDA, such as public seminars and FDA contracts with outside groups to study the feasibility of such labeling, the comments state that they have been assuming that the agency was carefully studying the concept of patient labeling and the problems inherent with it, and point to the November 7, 1975 FDA notice, which requested comments as to methods of drafting such labeling, as supporting that assumption. They argue that there is no medical or legal need to abandon this "reasonable" approach, particularly since the controversy in recent months over the appropriateness of estrogen therapy has served to highlight to physicians the complex medical problems of such therapy. Moreover, such a course of action may, they argue, constrict the agency in overall implementation of patient labeling requirements, such as proper modes of distribution, language and educational considerations and consideration of cost, if legal authority for patient labeling, which they argue does not currently exist, is obtained.

The Commissioner does not view the proposed requirement for patient labeling for estrogen drug products as conflicting with previously announced FDA policy. The November 7, 1975 notice clearly stated that the concept of patient package inserts is not an entirely new one to the agency. The notice also explained that FDA, in consultation with advisory committees and professional, trade, and consumer groups, was evaluating the usefulness of patient package inserts in order to establish an overall policy on patient labeling. The Commissioner did not, however, intend to imply that FDA would defer the adoption of requirements for patient labeling for specific drugs when the need for such labeling was clearly demonstrated. The Commissioner believes that such a need has been demonstrated for estrogen drug products. The advantages and risks associated with the use of these products are a type that can and should be assessed by patients, particularly the findings linking postmenopausal estrogen use to endometrial cancer, the reports of an association between intrauterine exposure to estrogens and congenital

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anomalies, and the finding of an increased risk of vaginal cancer in adolescent daughters exposed in utero to an estrogen (DES). Therefore, the Commissioner views the requirement for patient labeling for these drugs as not conflicting with previously announced FDA policy.

The Commissioner acknowledges at the same time, that there is still a proposal outstanding for a comprehensive plan for the development, issuance, and distribution of patient labeling for prescription drugs which, when issued in final form, may lead to modification of the patient labeling for oral contraceptives, estrogens, and other products for which earlier regulations were adopted.

6. *Inflationary aspects of the proposal.* Several comments questioned the statement in the preamble to the proposal that the Commissioner found that it would cause no major inflation impact. These comments argued that the requirement that bulk packages of estrogen products contain adequate numbers of patient package labeling would cause a substantial increase in cost for estrogen drug products. The comments argue that this requirement will necessitate in many instances that the outer carton be redesigned to provide sufficient space to accommodate the patient package labeling material. Because almost all packages will have to be redesigned, this will result in a one-time increase in cost. They argue further that the proposed regulation will also necessitate the redesign of machines used for machine packaging estrogen drug products. In many instances, it will make obsolete the manufacturers ability to use machines for final packaging, forcing the use of hand labor with a resultant increase in labor cost. Thus, depending on whether the machines can be adapted, or whether hand packaging will be required as an ongoing activity, the regulation will either cause a significant one-time cost increase or cost increases that will continue during the lifetime of the product. There will also be an increase in costs for pharmacists in terms of requirements for increased shelf space and for time to respond to patients' questions.

The comments also anticipate that many questions will be generated by the patient labeling and that the vast majority of these questions will be directed, appropriately, to the prescribing physician. Again, if the questions raised by the patient labeling become a burden upon the time available to the prescribing physician, he will have no other recourse than to charge the patient for the extra time needed to answer the patient's questions.

The Commissioner notes that neither the direct cost nor the indirect cost of the proposed requirements has been fully quantified. But the direct cost of printing package inserts and distributing them with the drug to the wholesaler and retailer and the cost of storage of these inserts appear to be very small. The Commissioner believes that the approximately 2.4 million dollars per year figure included in the agency's inflation impact assessment is a fairly accurate representation of the direct cost based on present rates of use. The Commissioner acknowledges that this approximate figure does not take into account the possibility that equipment used for machine packaging of estrogen drug products may have to be redesigned, or that in some instances the product may have to be hand packaged. In preparing the inflation impact assessment, however, the Commissioner did consider the slight increase in costs that result from the necessity of increased shelf space in the pharmacy. This is included in the 2.4 million dollar per year figure.

As estrogen patient labeling will be a new experience for patients, prescribers, dispensers, drug manufacturers and regulators, accurate predictions of the extent to which patient labeling will effect professional time demands are not possible. The past experience with oral contraceptive patient labeling, however, suggests that demands for professional time are not significantly increased by patient labeling. A conscientious physician presumably already advises each patient about the drugs that he prescribes—providing information on directions for use, cautioning against misuse, and giving warnings about possible adverse reactions. The patient labeling will simply reiterate this information and serve as a reminder for what the patient might forget. As experience is gained, physicians will be able to anticipate questions that might be stimulated by the patient labeling, and will be able to provide answers to these questions as part of the routine instructions provided to the patient. Thus, the Commissioner concludes that it is unlikely that the questions raised by the patient labeling will measurably lengthen the time of the patient's visit, except possibly in the case of a physician who is not accustomed to advising the patient about the drugs that are prescribed. The Commissioner notes, as well, that it is unlikely that the patient labeling will significantly burden pharmacists with an increase in questions regarding the drugs because the patient labeling specifically suggests that patients direct their questions to the prescribing physician.

7. *Availability of patient information on estrogens.* One comment contends that although patient labeling dispensed by pharmacists will help patients to some extent, the decision whether or not to prescribe the drug occurs in the doctor's office rather than in the pharmacy, and it is there that the patient most needs the information for discussing drug therapy. Moreover, the comment argues that if the patient has this information in hand while the decision is being made, the doctor has a strong incentive to be familiar with the contents of the various labels, and with the use of the drug in general. Once the patient has left the doctor's office, however, her opportunity to participate in the decision is gone, as is her opportunity to be sure the doctor is knowledgeable and careful about drug prescribing. Another comment recommends that the physician be required to provide the patient with the patient labeling at the time of prescribing, because the distribution of the patient labeling pieces to physicians by manufacturer representatives or by mail is less disruptive of the normal packaging procedures and may be less inflationary in the long run. The comment suggests that the storage and distribution of patient labeling pieces can be more easily managed in the doctor's office than in the pharmacy.

In response to this comment, the Commissioner notes that when the physician dispenses, or as in the case with injectables, administers the drug, he becomes the dispensor and under the regulation bears the responsibility for providing the patient with the patient labeling. In such cases the patient will be able to review the patient labeling at the time of administration, as recommended by the comment.

In other cases, however, which constitute the overwhelming majority, the patient labeling will be dispensed by the pharmacist along with the drug. The Commissioner views this result as the correct one.

The Commissioner agrees that the decision whether or not to prescribe a drug is usually made in the doctor's office. But this decision is made following examination and diagnosis. The physician would have to make a diagnosis, dispense the patient labeling, give the patient the opportunity to read the patient labeling and then discuss the advantages and disadvantages of estrogen therapy with the patient. Although the Commissioner would not object to this process, it is his opinion that the proper role of the patient labeling is to reinforce and augment oral information given by the physician. Furthermore, it is not reasonable to assume that physicians would have the available time and facilities commonly to engage in this process. Physicians have the primary responsibility to advise patients about drugs and provide such information as directions for use, cautions against misuse, and warnings about possible adverse reactions. Patient labeling should serve primarily as an adjunct to this discussion. Even when physicians elect to rely mainly on written communication of drug information to their patients, and where patient labeling will serve as a primary informational source to patients, that labeling still suggests that the patient make decisions regarding the use of the drug in consultation with her physician. The Commissioner concludes, therefore, that distribution by physicians would offer little advantage to the patient over obtaining the labeling from the pharmacist when the drug is dispensed.

The Commissioner disagrees with comments contending that for economic reasons physicians should distribute labeling. The Commissioner believes that labeling should be related to the distribution of the product. Such distribution provides for better control of the labeling in the channels of distribution in that the labeling can be tied into the

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product's lot-numbering system. This permits recall of labeling, if required, and assures that revised and updated labeling can be dispensed with those products packaged after the occurrence of a revision or an updating of the patient labeling. On the other hand, if labeling were provided only by physicians, it would be virtually impossible to update or recall obsolete labeling. It would also be necessary to send copies of revised labeling to every physician in the country. This would require excessive copies to be printed at additional cost and result in unnecessary distribution costs. Moreover, the Commissioner believes that pharamacies are more likely than doctor's offices to have the kinds of storage, access, and filing systems necessary for the efficient and reliable distribution of patient package inserts.

Finally, the Commissioner is of the opinion that the pertient sections of the act do not appear to authorize regulation of the prescribing function of physicians to the extent contemplated by the comment. The Commissioner does, however, strongly encourage the voluntary distribution of patient labeling by prescribing physicians. He urges manufacturers in their promotional campaigns to supply prescribing physicians with the patient labeling pieces and other supplies necessary to carry out the voluntary distribution program. As discussed above, when the physician dispenses, or (as in the case with injectables) administers the drug, he becomes the dispensor and under the regulation bears the responsibility for providing the patient with the patient labeling.

8. Ongoing distribution of patient labeling. One manufacturer suggested that § 310.515(d)(2), which requires each bulk package to include a sufficient number of patient-labeling pieces to assure that each patient package contain an insert, imposes unnecessary burdens and is inefficient. The comment suggests, for example, that pharmacists might remove the drug bottle from the carton or other enclosure for the patient-labeling pieces and inadevertently discard the carton with the patient labeling. The comment recommends that § 310.515(d)(2) be amended to permit the use of alternative methods of patient-labeling distribution. In particular, the comment urges that the use of a "pad system" be permitted. In this system the manufacturer or labeler would supply pads of patient labeling to the pharmacist for particular drug products along with instructions on how to order additional labeling. This system, it is argued, would be more efficient and effective in assuring that pharmacies have patient-labeling pieces available for inclusion with prescriptions.

The Commissioner believes that it is not desirable to separate the distribution of patient labeling from the shipment in bulk of estrogen drug products to the dispensor. Such a distribution system would increase the likelihood that the labeling would not be successfully tied into and connected with the drug product either in shipment or at the point of dispensing. The use of such a system, moreover, could result in the pharmacist (or physician, when he or she dispenses or administers the drug) either failing to dispense any patient labeling or in dispensing the wrong labeling. Finally, the Commissioner notes that traditionally, labeling has been included in bulk shipments of drug products and wholesale distributors and retail pharmacies have developed satisfactory procedures to ensure the proper distribution of the labeling. He is confident that manufacturers can devise packaging that will militate against pharmacists inadvertently disposing of enclosed labeling.

To prevent ambiguity, nonetheless, the Commissioner is amending § 310.515(d)(2) to indicate more clearly that in bulk packages intended for multiple dispensing, a sufficient number of patient labeling pieces must physically accompany the drug product, i.e., be included in or with each bulk package. The labeling pieces may be in individual or in "pad" form.

As a result of certain questions arising from activities of the agency, the Commissioner is further amending proposed § 310.515(d)(1) and (2) to make it clear that drug products dispensed or administered by physicians (e.g., injectables, etc.) are subject to these requirements, and that multiple-dose vials, like bulk packages intended for multiple dispensing, must also include in or with each package a sufficient number of patient-labeling pieces to assure that one piece can be given to every patient administered the drug.

The Commissioner expects that manufacturers and labelers will employ a reliable statistical method to determine the sufficiency of the number of patient-labeling pieces to be included in or with each bulk package and multiple-dose vial. He recognizes, however, that in some cases additional patient-labeling pieces may for a variety of reasons be required. The Commissioner is adding a sentence in § 310.515(d)(2) to indicate that the manufacturer or labeler may also employ a supplementary system to supply additional patient labeling to the dispensor. That system may not, however, act as a substitute for the requirement that patient labeling must be supplied in or with the bulk package.

9. Patient labeling and self-medication. One comment contends that a total patient package insert program that includes detailed information on indications for the use of drugs will result in the trading or exchanging of prescription medications by patients. A consumer may not understand that a specific drug has been prescribed for the sole purpose of treating that individual's illness. In some instances the results of such substitutions could be extremely harmful to the individual.

The Commissioner recognizes that this is a potential problem and that patients should be warned of the possible hazards of such a practice. The Commissioner agrees with this comment and is adding § 310.515(b)(8) accordingly.

10. Effect of patient labeling on patient compliance and suggestion-induced adverse reactions. Several comments expressed the opinion that patient labeling will greatly diminish patient compliance with dosage regimen. Consumers who learn of possible side effects, indications, and contraindications for a given medication may decide to discontinue or alter therapy without the benefit of medical advice. Alternatively, the comments suggest that patients may develop the suspected symptoms by suggestion.

The Commissioner believes that it is ultimately the patient's decision whether she wishes to take estrogens. Estrogen patient labeling should help patients make decisions about drug therapy on the basis of accurate and complete information. The factors behind patient adherence to agreed medication regimens are complex. With the present state of knowledge it is impossible to predict accurately the influence that patient labeling will have on adherence to agreed medication regimens.

Experience with oral contraceptive patient labeling suggests, however, that patient experience with drug therapy, rather than written information, primarily determines discontinuation of drug therapy. Furthermore, in the case of estrogens, the Commissioner firmly believes patients should take these drugs for as brief a period as possible and that women should be appraised of the reasons why this is the case. In the suggested wording of the patient labeling, patients are consistently referred to their physician so that decisions can be made in the context of appropriate medical advice.

If a patient decides to follow the instruction of her physician, the Commissioner does not believe that patient labeling will significantly increase the incidence of suggestion-induced side effects. Suggestion effects, moreover, seem to play a minimal role in determining serious adverse reactions. It is, in any event, possible to hypothesize beneficial as well as negative effects of suggestion. Clear expectations about the effects of drug therapy, reinforced by patient labeling, may make patients more sensitive and aware of certain physical or psychological reactions. Effects which might otherwise go unnoticed may be identified as drug related. Although this may have the effect of nominally increasing the reported incidence of less serious adverse reactions it also may have beneficial results. Patients may be more sensitive to "warning signals" of serious adverse effects. Accurate expectations may help reduce uncertainty and anxiety about possible effects of treatment. The patient may also be better able to interpret and identify more accurately the cause of drug-induced reactions, and treatment decisions will accordingly be based on more precise information. It is the Commissioner's opinion that the possible positive effects of supplying accurate side-effect information outweigh the possible negative effects.

At the same time, the Commissioner recognizes that there may be some drugs for which patient labeling is required and the physician concludes that the labeling should not be given to the patient—for

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example, where the patient would be adversely affected by some of the information in the patient labeling. The Commissioner does not, however, believe that estrogens fall into this category, and such option is not provided in this regulation.

11. *Flexibility in providing patient labeling in hospital settings.* A comment stated that hospitals and other health care institutions would require some flexibility in meeting the proposed requirements. It noted that the proposal is unequivocal; the "dispensor" must give labeling to the patient when an estrogen drug product is dispensed, or the drug will be deemed misbranded. The comment noted that in institutional health care, pharmacists, physicians, and nurses closely monitor a therapeutic course, and in that situation the patient can rely on personal contact and professional expertise for drug information to assure safe and effective therapy. The comment argued that hospital pharmacists be permitted to use professional discretion in determining the method of transmitting information, depending upon the seriousness of adverse affects, the condition of the patient, and the frequency with which the drug will be administered. The comment further argued that it would be impractical for a hospital using a unit-dose drug distribution system to provide patient labeling whenever a drug is dispensed, because the drug is dispensed one dose at a time. The comment recommended, therefore, that the regulation permit acute care hospitals to provide patient labeling to inpatients on estrogen therapy before administration of the first dose of estrogen, and in long-term care facilities, before the first administration and every 30 days thereafter. The comment also urged that if clinical services substantially furnish the information called for, misbranding should not be deemed to occur if the actual labeling were not provided.

The Commissioner agrees that hospitals and other health care institutions should have some flexibility in meeting the requirements of this regulation. He concludes that it would be impractical and unnecessary to require patient labeling to be made available to the hospitalized patient every time a drug is administered. Therefore, the final regulation is revised by adding a new sentence to § 310.515(d)(1) that states that the requirements of § 310.515 are met in the case of estrogen drug products prescribed in an acute care hospital or in long-term facilities if the patient labeling is provided to the patient before administration of the first dose of estrogen and every 30 days thereafter as long as the therapy continues.

However, the Commissioner does not agree that clinical services should be permitted to merely "substantially" convey the information called for in this proposal. He advises that the requirement for patient labeling for this drug product cannot be satisfied by oral communication of the information by either the pharmacist or physician. The written patient labeling is intended to be a supplement to any oral communication of this information, or in the absence of any oral communication, to at least furnish the patient with basic information necessary for the patient's safe and effective use of the product.

12. *Type size in patient labeling.* Comments were received objecting to the proposed requirement that 9-point (noncondensed) type be used in patient labeling. One comment contended that the requirement for 9-point type is not a valid method of specifying type height or legibility. The comment argued that an 8-point type face may in some cases be significantly more legible and easier to read than some 9-point faces. The comment further pointed out that the 9-point type is not a standard size (the standards for type size are 6, 8, 10, and 12 point) and, therefore, is not available in many different type faces and styles. Mandating a 9-point size requirement will, therefore, complicate machine finishing and will not permit many of the procedures that are currently being followed by manufacturers to be applied to patient labeling. It could, for example, make it necessary to redesign bulk package outer cartons, result in larger cartons, and increase the amount of shelf space needed to store the drug product in the pharmacy. The comment recommends that the regulation not specify a minimum type size, but instead contain language requiring that the patient labeling be legible.

The Commissioner has given further consideration to the question of type size and legibility of patient labeling and has concluded that language requiring only that the labeling be "legible" would be unduly vague. A more objective standard that can be uniformly applied to all patient labeling is necessary. Therefore, a minimum type size must be established. The Commissioner is, however, persuaded that specifying a particular point type size is not, by itself, a valid method of specifying type height or legibility. Accordingly, the final regulation is revised to specify that the minimum type size shall be at least $\frac{1}{16}$ inch in height. The height pertains to lower case letters, and it is the lower case "o" or its equivalent that shall meet the minimum standard. The body copy shall be 1-point leading and noncondensed type, and shall not contain any light face type or small capital letters. It is the opinion of the Commissioner that this requirement will result in a type size that will ensure legibility without imposing a significant burden on the manufacturer.

13. *Effective date provisions.* Comments were received objecting to the provision in the proposed regulation that would allow estrogen drug products in the possession of a wholesaler or retailer before the effective date to be shipped or sold if adequate numbers of copies of the patient labeling are furnished to the wholesaler or retailer to permit any retail purchaser after the effective date to obtain such labeling with the product. The comments suggested that this section be deleted and that the effective date be predicated upon the date on which the estrogen drug products are packaged. They argued that distribution of the patient labeling separate from the product is inappropriate since control of labeling is lost. An opportunity also exists that one manufacturer's package labeling may inadvertently be given to a patient when in fact another manufacturer's product was dispensed. The proposed process would also provide no means of revising the labeling or alerting the retailer that the patient labeling has been revised or otherwise updated.

The Commissioner does not believe that it would be in the best interest of the patient to establish as the effective date of the regulation the date on which the products are packaged. That choice would afford manufacturers the opportunity to stockpile supplies of the drug not containing patient labeling, and could result in significant delays in providing the patient with the labeling. It could also result in a wide variation regarding the time when the products of various manufacturers would begin to be furnished to patients with patient labeling. The intent of the effective date provision as proposed is to prevent any further distribution of the subject drug without patient labeling on or after the effective date, without requiring the recall of stock in possession of persons who are not responsible for the content of the labeling, i.e., wholesalers or retailers. The distribution of patient labeling separate from the product on an interim basis will assure the prompt availability of the patient labeling as of the effective date of the final regulation, thus avoiding the necessity of a recall. Although a physician who dispenses or administers the drug is considered to be a retailer under the regulations, the Commissioner has concluded that it would be impractical to require the forwarding of separate patient labeling, within the specified time frame, to such physicians for those products in their possession before the effective date. Accordingly, the requirement that any estrogen drug product be dispensed with patient labeling, as applied to physicians who dispense or administer the drug, will not be effective for supplies in their possession on the effective date, but will apply only to supplies received thereafter.

14. *Applicability of the proposed regulation.* One comment expressed the concern that the proposal, although obviously intended to apply only to estrogen drug products that are restricted to prescription distribution, did not clearly state that the proposal is not applicable to over-the-counter drugs or cosmetics. The comment requested that the Commissioner expressly state that proposed § 310.515 is only applicable to prescription drugs.

The comment is correct in stating that the proposal only applies to estrogen drug products that are restricted to prescription distribution. The final regulation is revised in § 310.515(a) to include a specific statement to that effect.

The Commissioner advises that he is not aware of any over-the-counter estro-

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gen drug product intended for internal use. There are, however, several over-the-counter estrogen-containing drug products intended for topical use. These preparations, currently being reviewed by the OTC Advisory Review Panel for Miscellaneous External Products, will not be affected in any way by this regulation.

15. *Content of patient labeling: § 310.515(b) of the proposed rule.* Section 310.515(b) of the proposal prescribes certain specific points of information that shall be included in the patient labeling. Several comments were received on those points of information. The most significant comments and the Commissioner's response to those comments follow.

a. One comment recommended that endorsement of estrogen for short-term use for moderate vasomotor symptoms of menopause be deleted from § 310.515(b)(3). In the opinion of the comment, the patient information should not recommend estrogens for anything but the most severe and incapacitating vasomotor symptoms—otherwise known as "hot flashes." The comment argued that for estrogen use to be suggested merely because the patient is going through menopause is unacceptable, considering the unequivocal animal and human evidence that estrogens cause cancer.

The Commissioner responds that, although the labeling allows for the use of estrogens for moderate vasomotor symptoms, the labeling is not intended to suggest that estrogen use is appropriate merely because the patient is going through menopause. While "moderate" and "severe" are subjective terms, and may have different meanings to physicians and patients, the Commissioner believes the labeling clearly indicates that a significant symptom is necessary to justify use. For the type of vasomotor symptoms (hot flashes) for which estrogens are indicated there is no alternative therapy, and such therapy is intended for short-term use only. With these considerations in mind the Commissioner concludes that to limit the use to severe vasomotor symptoms would be unnecessarily restrictive, and that the regulation should not be revised in this respect.

b. A comment objected to the statement in proposed § 310.515(b)(3) that estrogens are not indicated for the treatment of nervousness. The comment contends that a number of investigators have studied the effects of estrogen on emotional symptoms associated with the menopause and generally have found estrogens beneficial in alleviating such conditions. Such studies have included several double-blind studies, e.g., those by Douglas (Medical Annals of the District of Columbia, 38:437, 1969), Sheffrey (Medical Annals of the District of Columbia, 38:433, (1969), and Lozman, et al. (Southern Medical Journal, 46: 1079, 1972). In addition, it is argued, studies by Klaibern, et al. (American Journal of Psychiatry, 128:1492; and Conference on Biorhythm and Human Reproduction, New York, October, 1972) have shown that conjugated estrogens are effective in alleviating depression in women, probably because of restoration in initially depressed patients of more normal levels of essential adrenergic functioning. The comment concludes that there is sufficient evidence that estrogens are effective in alleviating certain nervous symptoms or depression that may occur during the menopause, and that a statement to the contrary is inappropriate.

The Commissioner is familiar with the references cited by the comment, but does not agree that the studies offer substantial evidence that estrogens are effective for the treatment of nervousness. Estrogens have been shown to be effective in treating moderate to severe vasomotor symptoms. In the presence of such symptoms many women also exhibit signs of nervousness or depression. It is the Commissioner's view that it is the successful treatment of the vasomotor symptoms that removes the cause of the nervousness and depression; hence, these symptoms are alleviated. He notes, moreover, that there is no evidence that estrogens are effective in alleviating nervous symptoms or depression that are not caused by conditions for which estrogens have been shown to be effective.

c. A comment was received in regard to the terminology "cancer of the uterus" used in § 310.515(b)(4)(i). The comment contends that the correct term is "endometrial carcinoma," and not "cancer of the uterus," which includes cervical as well as other types of cancer.

The Commissioner agrees with this comment and § 310.515(b)(4)(i) is revised accordingly.

d. A number of comments expressed concern regarding the risk of endometrial carcinoma (cancer of the uterus) for women who have had hysterectomies. They suggested that neither the proposed rule nor the labeling text adequately addressed this issue.

To allay any unnecessary concerns, the final rule is revised to require a statement in the patient labeling that indicates that women who have had total hysterectomies have no risk of endometrial carcinoma.

e. One comment contended that the patient labeling should mention "liver tumors" and not "benign liver tumors" as proposed by § 310.515(b)(6). The comment argues that although the majority of tumors associated with estrogen use as reported in the published literature have been classified as "benign," some tumors have been classified as malignant. Moreover, it is argued, those tumors classified as "benign" have malignant potential if not surgically excised. The comment suggests that use of the term "benign" when there is malignant potential, and where malignant liver tumors have also occurred in oral contraceptive users, is deceptively soothing to the ordinary consumer.

The Commissioner agrees that although the majority of tumors associated with estrogen use as reported in the published literature have been classified as benign, some tumors associated with the use of estrogen containing oral contraceptives have been classified as malignant. The Commissioner believes that deleting the word "benign" would be more accurate under the circumstances. The regulation is revised accordingly.

DATE OF MOST RECENT REVISION

The Commissioner is revising § 310.515(b)(8) to provide that the date, identified as such, of the most recent revision of the labeling be prominently placed immediately after the last section of the labeling. This conforms to the present practice of many manufacturers and should, therefore, not be disruptive of labeling processes.

STATUS OF PATIENT LABELING TEXT: REVISIONS OF OCTOBER GUIDELINE

Section 310.515(f) requires that FDA make available and publish in the FEDERAL REGISTER patient labeling for estrogens that is responsive to all items specified in § 310.515(b). The suggested text of patient labeling that met the requirements of the proposed rule was published in the FEDERAL REGISTER of September 29, 1976 (41 FR 43117) and revised in the FEDERAL REGISTER of October 29, 1976 (41 FR 47573). In this final regulation, as a result of comments received on proposed § 310.515(b), the Commissioner is making a number of rule changes and determines that corresponding changes in the patient labeling text are necessary.

Published elsewhere in this issue of the FEDERAL REGISTER is the precise language of the revised patient labeling text that will be considered to meet the requirements of the final rule. The Commissioner advises that the text of the patient labeling is intended as a guideline (21 CFR 10.90) which if followed will enable any person to comply with the requirements of § 310.515(b).

Those manufacturers and suppliers who have deferred preparing patient labeling until the publication of the final rule have until September 20, 1977, to implement the revised labeling requirement. For those manufacturers and suppliers who put into use the October 29, 1976 patient labeling text prior to the issuance of the final order, the October labeling will continue to be considered by the Commissioner as meeting the requirements of § 310.515(b) until November 21, 1977. After November 21, 1977, the labeling text published on October 29, 1976 can no longer be relied upon as meeting the requirements of § 310.515(b).

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 701(a), 52 Stat. 1050–1053 as amended, 1055 (21 U.S.C. 352, 355, 371(a))) and under authority delegated to the Commissioner (21 CFR 5.1), Part 310 is amended by adding new § 310.515 to Subpart E, to read as follows:

§ 310.515 Estrogens; labeling directed to the patient.

(a) The Commissioner of Food and Drugs concludes that the safe and effective use of drug products containing estrogens requires that patients be fully informed of the benefits and risks involved in the use of these drugs. Accordingly, except as provided in paragraph

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(e) of this section, each estrogen drug product restricted to prescription distribution, including products containing estrogens in fixed combination with other drugs, e.g., estrogen-tranquilizer combinations, that is the subject of a new drug application approved either before or after the Drug Amendments of 1962 and any identical, related, or similar drug product, whether or not it is the subject of an approved new drug application, shall be dispensed to patients with labeling in lay language containing information concerning effectiveness, contraindications, warnings, precautions, and adverse reactions. The patient labeling shall be provided as a separate printed leaflet independent of any additional materials.

(b) The patient labeling shall specifically include the following:

(1) Name of the drug.

(2) Name and place of business of the manufacturer, packer, or distributor.

(3) A statement regarding the proper use of estrogens, particularly short-term use in moderate to severe vasomotor symptoms of the menopause and prevention of breast engorgement. It is to be stated that estrogens are not indicated for certain conditions, i.e., nervousness, preservation of supple skin, or maintenance of a youthful feeling. The limited usefulness in preventing breast engorgement is also to be noted.

(4) A warning regarding the most serious dangers of estrogens and the relative risk in users versus nonusers, where known, including:

(i) Endometrial carcinoma. The importance of minimizing dose and duration of use is to be stressed, as is the importance of using estrogens only when necessary. A statement indicating that women who have had total hysterectomies have no risk of endometrial carcinoma.

(ii) Other possible cancer. The importance of annual examinations is to be stressed. Special attention to women with breast nodules, adnormal mammograms, or a family history of breast cancer is to be mentioned.

(iii) Gall bladder disease.

(iv) Abnormal blood clotting.

(v) Damage to exposed fetus.

(5) A statement of contraindications.

(6) A discussion of other side effects of estrogens, including oral contraceptives, such as nausea and vomiting, breast tenderness, growth of fibroids, liver tumors, jaundice, mental depression, fluid retention, and darkening of the skin.

(7) A discussion of the danger signs of which the patient must be aware, including abnormal vaginal bleeding, symptoms suggesting thrombophlebitis, pulmonary embolus, stroke or heart attack, breast lumps, jaundice, and depression.

(8) A statement cautioning the consumer that this drug has been prescribed for the sole purpose of treating the individual's illness and that the drug must not be given to others.

(9) The date, identified as such, of the most recent revision of the labeling prominently placed immediately after the last section of such labeling.

(c) The patient labeling shall be printed in accordance with the following specifications:

(1) The minimum letter size (lowercase letter "o" or its equivalent) shall be not less than 1/16 inch in height.

(2) The body copy shall contain 1-point leading and noncondensed type, and shall not contain any light face type or small capital letters.

(d) (1) Patient labeling for each estrogen drug product shall be provided in or with each package of the drug product intended to be dispensed or administered to the patient. However, patient labeling for drug products dispensed in acute care hospitals or long-term-care facilities will be considered to have been provided in accordance with this section if provided to the patient prior to administration of the first dose of estrogen and every 30 days thereafter, as long as the therapy continues.

(2) In the case of estrogen drug products in bulk packages intended for multiple dispensing, and in the case of injectables in multiple-dose vials, a sufficient number of patient labeling pieces shall be included in or with each package to assure that one piece can be included with each package or dose dispensed or administered to every patient. Each bulk package shall be labeled with instructions to the dispensor to include one patient labeling piece with each package dispensed or, in the case of injectables, with each dose administered to the patient. This section does not preclude the manufacturer or labeler from distributing additional patient labeling pieces to the dispensor.

(3) Any estrogen drug product restricted to prescription distribution, except as noted in paragraph (c) of this section, that is not labeled as required by this section and that is either introduced or delivered for introduction into interstate commerce, or held for sale after shipment in interstate commerce is misbranded pursuant to section 502 of the act. However, an estrogen drug product in the possession of a wholesaler or retailer before the effective date of this section is not misbranded if adequate numbers of copies of the patient labeling are furnished to the wholesaler or retailer to permit any retail purchaser after the effective date to obtain such labeling with the product. The requirement that any estrogen drug product be dispensed with patient labeling, as applied to physicians who dispense or administer the drug, will not be effective for supplies in their possession on the effective date, but will apply only to supplies received thereafter.

(e) This section does not apply to estrogen-progestagen oral contraceptives and oral diethylstilbestrol (DES) products intended for postcoital contraception, which shall be labeled according to the requirements of § 310.501.

(f) The Food and Drug Administration has available patient labeling for estrogens that includes information responsive to all items specified in paragraph (b) of this section. The labeling has been published in the FEDERAL REGISTER as part of a DESI notice, and updated versions will continue to be published as guides as changes occur. Any person may rely on the latest published version of this labeling as complying with paragraph (b) of this section.

(g) Holders of new drug applications for estrogen drug products that are subject to this section must submit supplements under § 314.8(d) of this chapter to provide for the labeling required by paragraph (a) of this section. The labeling may be put into use without advance approval by the Food and Drug Administration.

Effective date: This regulation shall be effective on September 20, 1977.

(Secs. 502, 505, 701(a), 52 Stat. 1050–1053 as amended, 1055 (21 U.S.C. 352, 355, 371(a)).)

Dated: July 15, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc.77-20020 Filed 7-21-77;8:45 am]

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